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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/955,174	09/19/2001	William G. Kerr	USF-T150CX	9411

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/955,174	KERR, WILLIAM G.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38-44,46-66,74-87 and 90-94* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38-44,46-66,74-87 and 90-94* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6-26-07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communications filed 6-26-07.

Claims 38-44, 46-66, 74-87 and 90-94 are pending in the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6-26-07 has been entered.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Claims 38-44, 46-66, 74-87 and 90-94 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons of record set forth the Office actions mailed 5-5-05, 12-29-05, 9-26-06, 3-30-07, and for

the reasons set forth below. This is both a new matter rejection and a written description rejection, and the arguments for maintaining both grounds of rejection are set forth below.

The claims are drawn to compositions and methods for reducing SHIP-1 function in human or mouse hematopoietic cells in vivo, and for suppressing rejection of a transplant in a human or mouse comprising the administration of an efficacious amount of any means for inhibiting SHIP-1 function, which means interferes with translation of any SHIP-1 RNA, or comprising administration of any interfering RNA (RNAi) specific for, or hybridizable with, any SHIP-1 mRNA that is present in human or mouse hematopoietic cells, which RNAi hybridizes in vitro under "conditions of stringency" with human or mouse SHIP-1 mRNA or hybridizes in vivo with SHIP-1 mRNA present in mouse or human hematopoietic cells and reduces SHIP-1 function in human or mouse, suppresses graft-versus-host disease in a mouse or human, and suppresses transplant rejection in a human or mouse.

Applicant's arguments filed 6-26-07 have been fully considered but they are not persuasive. Applicant argues that the new matter rejection is improper because the lack of disclosure of RNAi molecules in the original disclosure is not determinative of whether the claimed subject matter represents new matter. According to Applicant, the subject specification taken as a whole would lead one of ordinary skill in the art to use RNAi molecules that interfere with expression of SHIP-1 mRNA despite the fact that RNAi was not explicitly disclosed in the original specification. Applicant also requests that the Examiner indicates whether or not she is taking official notice of the common

usage of the term "interfering" in connection with transcription and/or translation of a target gene's RNA, and that the means for interfering with transcription and/or translation of SHIP RNA encompasses a genus of various inhibitors. Indeed she is. But whether or not this is so, Applicant still fails to overcome the new matter rejection.

Applicant is correct that various inhibitory molecules are encompassed by the term "interfering" in connection with transcription and/or translation of a target gene's RNA. But, contrary to Applicant's assertions, unless the newly discovered RNAi inhibitors were explicitly disclosed at the time of filing, no assumption can reasonably be made that the disclosure meant to include this fairly new class of inhibitory molecules.

Applicant admits that antisense, aptamers and ribozymes were specifically mentioned in the original specification. In stark contrast, however, the omission of the term RNAi (or SiRNA) from the original disclosure is hard to ignore, and therefore leads one to the conclusion that these specific type of inhibitory molecules were not contemplated at the time of filing the original disclosure. Applicant is correct that antisense, ribozymes and aptamers are specifically mentioned in the instant disclosure. There is, however, no SPECIFIC MENTION of RNAi molecules or RNAi inhibition in the original application. No examples were provided in the instant specification, either prophetic or actual, mentioning the existence of RNAi, in contrast to the mention of the other inhibitory molecules, antisense, ribozymes and aptamers.

Applicant also argues that claims 74-87 and 90-94 do not recite the term "interfering RNA" and therefore find literal support in appropriate portions of the original specification and therefore are not properly rejected under a new matter rejection.

Applicant is correct concerning this particular point. The claims, however, encompass a broad genus of inhibitory molecules (even if they exclude RNAi in light of the original specification), and therefore are rejected for inadequate written description, not for containing new matter.

Applicant argues that adequate written description is provided for the broad genus of inhibitory compounds claimed because there would be no difficulty in identifying target mRNA sequences shared by all known hematopoietic SHIP-1 isoforms in humans and mice, due to an extensive amount of sequence overlap between the isoforms, and in light of the enzymatic domain, inositol 5'-phosphatase, that exists in the various isoforms.

Contrary to Applicant's assertions, however, the ability to envision target nucleic acid sequences does not necessarily provide a concise description of the features of a representative number of species of the broad genus claimed, that were in Applicant's possession at the time of filing, and that performed the functions claimed, of providing in vivo effects following their administration to an organism.

The instant application claims a priority date of 9-19-00. Applicant, in arguing that adequate written description was provided at the time of filing for the genus of inhibitory molecules claimed, provides numerous post-filing publications that disclose how RNAi molecules are generated in cells from longer double stranded molecules. It is unclear how these post-filing publications can be used - in retrospect - to confer adequate written description onto a previously filed application. Applicant filed an IDS on 10-7-05, well after the filing date of the original application, referencing the

pioneering work by Fire, Elbashir and others concerning RNAi. These post-filing examples, however, do not provide proper support for RNAi in the application as originally filed. Post-filing amendments to the claims do not compensate for this deficiency either, as asserted previously by Applicant.

Furthermore, the declaration filed later in prosecution, on 7-21-04, provides a disclosure of experiments in which SiRNA (*a.k.a.* interfering RNA or RNAi) molecules #1, 2, 3 and 4, or a combination or subcombination of them, were found to successfully inhibit the expression of SHIP-1 in vitro and in vivo. The original application, however, does not provide disclosure of these SiRNA molecules, nor of these experiments, nor of any mention of interfering RNA molecules in general. The existence of publications, provided in the supplemental IDS (filed 10-7-05) with various references teaching RNAi molecules and their use in RNAi-mediated gene suppression in mammalian cells, does not compensate for the failure to provide support for RNAi in the original application.

Applicant argues that adequate written description has been provided for the broad genus claimed, comprising any interfering RNA (RNAi) specific for SHIP-1 mRNA that is present in human or mouse hematopoietic cells, which RNAi hybridizes in vitro under conditions of stringency with human or mouse SHIP-1 mRNA or hybridizes in vivo with SHIP-1 mRNA present in mouse or human hematopoietic cells and reduces SHIP-1 function in human or mouse, suppresses graft-versus-host disease in a mouse or human, and suppresses transplant rejection in a human or mouse.

Applicant argues that the disclosure at time of filing reasonably conveys to one of ordinary skill in the art that the Applicant had possession of the subject matter claimed.

Applicant again refers to the teachings provided in the supplemental IDS (filed 10-7-05), citing various references teaching RNAi molecules and their use in RNAi-mediated gene suppression in mammalian cells. Applicant additionally argues that structural attributes of interfering RNA, including size and content, were known in the art at the time of filing.

Contrary to Applicant's assertions, the instant disclosure does not adequately describe the concise structural features that distinguish structures within the claimed genus from those without (*e.g.* the nucleotide sequences or a representative number of RNAi molecules of the generic RNAi structures claimed, that specifically bind and inhibit SHIP-1 function in vivo, and which suppress graft-versus-host disease and transplant rejection). The description provided of the target molecules claimed and the subsequent description of two RNAi constructs (filed 7-21-04) that provide for the functions claimed, of reducing SHIP-1 function in human or mouse hematopoietic cells in vivo, and of suppressing rejection of a transplant in a human or mouse, are not representative of the broad genus comprising RNAi that hybridize in vivo with SHIP-1 mRNA present in hematopoietic cells of the human or mouse and reduce SHIP-1 expression therein. The subsequent disclosure of two species within the broad genus of RNAi molecules claimed, that, when combined provide for the treatment effects claimed, are not representative of the very broad genus of inhibitory molecules claimed.

The specification and claims do not adequately describe the concise structural features that distinguish structures within the claimed genus from those without (*e.g.* the exact nucleotide sequences or a representative number of RNAi molecules of the

generic RNAi structures claimed, that specifically bind and inhibit SHIP-1 function in vivo, and which suppress graft-versus-host disease and transplant rejection).

Applicant also argues that adequate written description for the broad genus of compounds claimed has been provided since the screening of RNAi candidates in vitro for their ability to target and inhibit expression of the known target gene was routine at the time of filing.

Contrary to Applicant's assertions, the ability to screen candidate inhibitory molecules for their ability to inhibit target gene inhibition in vitro is merely an invitation to experiment further to identify RNAi that exhibit inhibitory activity. The invitation to experiment does not convey possession at time of filing, and hence does not satisfy written description requirements for the broad genus of compounds claimed.

One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of the inhibitory molecules claimed, encompassing the genus comprising RNAi specific for SHIP-1 mRNA present in human or mouse hematopoietic cells or comprising any nucleic acid molecule (and of any size) that hybridizes in vitro under "conditions of stringency" with human or mouse SHIP-1 mRNA or hybridizes in vivo with SHIP-1 mRNA present in mouse or human hematopoietic cells and provides the treatment effects claimed.

For these reasons, the instant 35 U.S.C. 112, first paragraph rejection, for lacking adequate written description and for failing to provide adequate support for RNAi in the originally filed application, is hereby maintained.

Claims 38-44, 46-66, 74-87, 90-92 and 94 are rejected under 35 U.S.C. 112, first paragraph, for lacking enablement over the scope claimed for the reasons of record set forth the Office actions mailed 5-5-05, 12-29-05 and 9-26-06, 3-30-07, and for the reasons set forth below.

The claims are drawn to methods for interfering and reducing SHIP-1 function in a human or mouse, for suppressing transplant rejection in a human or mouse, and for suppressing graft versus host disease (GVHD) in a human or mouse comprising the administration any RNAi specific for SHIP-1 mRNA present in human or mouse hematopoietic cells, or which RNAi hybridizes in vitro under "conditions of stringency" with human or mouse SHIP-1 mRNA or hybridizes in vivo with SHIP-1 mRNA present in mouse or human hematopoietic cells.

The instant disclosure, while being enabling for a method of suppressing the rejection of an allogeneic bone marrow graft from BALB/C mice in SHIP-/- mice or abrogating GVHD disease in SHIP-/- mice that were transplanted with whole bone marrow from BALB/C mice, thereby enhancing SHIP-/- mice survival, and while being enabling for the in vivo inhibition of SHIP-1 expression in mice using the RNAi sequences #1, #4 and the mouse antisense vector muSHIPshRNA provided in the declarations by Dr. Kerr, filed 7-21-04 and 2-9-05, does not reasonably provide enablement for inhibiting SHIP-1 in vivo comprising the administration of *any* RNAi specific for SHIP-1 mRNA present in human or mouse hematopoietic cells, or comprising the administration in vivo or ex vivo of *any* nucleic acid molecule that hybridizes in vitro under conditions of stringency with human or mouse SHIP-1 mRNA

or that hybridizes in vivo with SHIP-1 mRNA present in mouse or human hematopoietic cells, nor of suppressing a transplant rejection in any patient, or treating graft versus host disease (GVHD) in any patient comprising the administration of any interfering RNA specific for SHIP mouse or human mRNA.

Applicant's arguments filed 6-26-07 have been fully considered but they are not persuasive. Applicant argues that the full scope of the claims is enabled for several reasons. Applicant argues that the specification as filed taught the suppression of the rejection of an allogeneic bone marrow graft from BALB/C mice in SHIP-/- mice, as well as the abrogation of GVHD disease in SHIP-/- mice that were transplanted with whole bone marrow from BALB/C mice, whereby SHIP-/- mice survival was enhanced. Applicant also argues that the declarations subsequently filed on 7-21-04 and 2-9-05 taught the in vivo inhibition of SHIP-1 following the co-administration of two species of RNAi sequences, #1, #4, or following the administration of the mouse antisense vector muSHIPshRNA. Applicant also argues that a specification is initially presumed to be enabled, the burden is on the Patent Office to establish a reasonable basis to question enablement, and that complete inhibition of target gene expression is not necessary to provide treatment effects. Applicant also argues that prior Office actions have not stated what guidance is missing from both the subject specification and the art that is necessary to carry out the invention without resorting to undue experimentation.

Applicant is correct that complete inhibition is not necessary to provide for the treatment effects claimed. But, contrary to applicant's assertions, the instant rejection is not being made because complete inhibition is being demanded in order to fulfill the

enablement requirement. Enablement standards are met when a representative number of species from the broad genus of inhibitory compounds claimed have been shown to provide treatment effects following their administration to the organism. The success of delivery of other inhibitory molecules, in other organisms, to target and inhibit other target genes, and to treat other conditions, is not representative of the ability to provide the treatment effects using the instantly claimed compounds. One cannot extrapolate the success of others to the instantly claimed invention. The state of the art of gene therapy in an organism, at the time of filing the instant application, was still a highly unpredictable endeavor, requiring undue experimentation beyond that taught in the instant disclosure, to provide for the treatment effects claimed using the broad genus of compounds claimed.

And, contrary to Applicant's assertions, the ability of two species of the broad genus of compounds claimed, which were co-administered RNAi's, or of the mouse antisense vector muSHIPshRNA to target and successfully inhibit expression of the target gene encoding SHIP1 in a mouse model, and provide for an observed increase in Mac+Gr1 monocytes and circulating Mac1+GR1+cells (myeloid suppressor cells) are not representative or correlative of the ability to achieve in vivo SHIP-1 inhibition of expression or subsequent treatment effects comprising the administration of <u>any</u> RNAi specific for, or hybridizable with any SHIP-1 mRNA present in human or mouse hematopoietic cells or comprising any nucleic acid molecule (and of any size) that hybridizes in vitro under conditions of stringency with human or mouse SHIP-1 mRNA

or hybridizes in vivo with SHIP-1 mRNA present in mouse or human hematopoietic cells.

The examples provided using three species of inhibitory molecules, are not representative, and are not enabling for the ability to provide for in vivo treatment effects claimed using the broad genus of compounds claimed.

Applicant argues further that RNAi is distinguishable from antisense and ribozymes because less RNAi are required for effective inhibition of target genes. Applicant is correct that investigators have reported that lower concentrations of RNAi molecules are likely needed for effective inhibition in a target cells compared to antisense or ribozyme molecules (*see e.g.* Fire (USPN 6,506,559, at col. 3). However, contrary to Applicant's assertions, while lower concentrations of RNAi molecules are likely required in target cells for effective target gene inhibition in comparison to antisense or ribozymes, in vivo efficacy of RNAi still depends on the effective delivery of threshold concentrations of these oligonucletides sufficient to silence the target gene in target cells harboring the SHIP-1 target gene, and in vivo delivery of oligonucleotides, whether they be antisense, ribozymes or RNAi molecules, is generally a highly unpredictable endeavor at the current time.

Applicant is again reminded that the state of the art has been reflected in the publication of record of Caplen, in a recent review article concerning RNAi as an effective gene therapy tool (Caplen, N.J., Expert Opinion Biol. Ther., Vol. 3, No. 4, pages 575-586, 2003, esp. the bridging paragraph, at pp. 577-8), who addressed the unpredictability regarding predicting efficacy of RNAi molecules: "While most siRNAs

are effective in inducing some degree of gene silencing, there are wide ranges in the efficacy of individual siRNAs against sequences within the same gene, and some siRNAs show limited or no ability to mediate RNAi. It is currently unclear what specific parameters determine the effectiveness of a given siRNA and, thus, why some sequences may be better targets than others." See also Caplen at p. 581: Many of the problems associated with developing RNAi as an effective therapeutic are the same as encountered with previous gene therapy approaches. The key issues of delivering nucleic acids to the required tissue and cell type, while ensuring an appropriate level of efficacy with minimum toxicity induced by the vector system have been problems the gene therapy field has struggled with for over a decade now."

The phenotypes that are obtained in ablation models do not circumvent the problems of unpredictability associated with delivery issues, and these delivery hurdles exist to this day. Phenotypes that may be displayed in ablation models are not predictive of the ability to deliver adequate quantities of RNAi, or other members of the genus of inhibitory molecules claimed, to an appropriate target cell in vivo, and provide for the treatment effects claimed. While partial suppression of SHIP expression has been shown to provide for the treatment effects instantly claimed, only two candidate RNAi molecules have been shown to provide for even partial inhibition of expression. For these reasons, the instant rejection for lacking enablement over the scope claimed, is maintained.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the

Group is 571-273-8300. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jane Zara whose telephone number is (571) 272-0765. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz, can be reached on (571) 272-0763. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
8-31-07

TC 1600
JANE ZARA, PH.D.
PRIMARY EXAMINER